REMARKS

In the Office Action dated August 1, 2006, claims 1-38 are pending. Claims 28-38 are withdrawn from consideration. Claims 1-27 are under examination and are rejected.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In the Action, the Examiner has objected to the oath for omitting the post office address for the fourth inventor. Applicants will provide this information as soon as such information becomes available.

In the claims, Applicants have amended claim 1 to incorporate the features of claims 5-6, i.e., the strain of claim 1 is presently characterized to co-express α-1,2-mannosidase, GnT1 and GalT or functional parts of these enzymes, and has a disrupted Och1 gene. The α-1,2-mannosidase of claim 1 is also further defined as a *Trichoderma reesei* α-1,2-mannosidase (previous claim 9). Claims 5-9 have been canceled in view of the amendment to claim 1. Applicants reserve the right to pursue the subject matter embodied in the original claims in a continuation application.

Claims 1-4 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The Examiner contends that the term "genetically engineered methylotrophic yeast strain" does not define the genetic modification.

Applicants respectfully submit that the genetically engineered methylotrophic yeast strain, as previously claimed, is clearly characterized by its ability to produce glycoproteins comprising a mammalian-like N-glycan structure. The mammalian-like N-glycan is further

characterized in the claim as containing five or fewer mannose residues and at least one N-acetylglucosamine residue (GlcNAc) which is linked to a mannose residue and to a terminal galactose residue. As the Examiner has correctly recognized, the modifications required to produce the strain can be achieved in various ways. Applicants respectfully submit that the strain, as previously claimed, is clearly defined to those skilled in the art and does not require any further characterization of the specific genetic modifications. However, in an effort to favorably advance prosecution of the present case, Applicants have amended claim 1 to incorporate the features of previous claims 5-6. Present claim 1 specifically delineates the genetic modifications contained in the strain, i.e., the strain expresses a *Trichoderma reesei* α-1,2-mannosidase or a functional part thereof, a GnTI or a functional part thereof, and a GalT or a functional part thereof, and contains a disrupted genomic OCH1 gene.

In view of the foregoing, Applicants respectfully submit that the rejection of claims 1-4 under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-4, 6 and 27 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Specifically, the Examiner acknowledges that the specification discloses a genentically engineered *Pichia pastoris* strain that produces a glycoprotein comprising a specific mammalian-like N-glycan structure, such as $GalGlcNAcMan_5GlcNAc_2$. However, the Examiner contends that the specification does not describe the genetic modifications required to produce the specific genetically engineered strain in the absence of enzymes required to modify the N-glycan structure of glycoproteins or in the presence of a functional OCH1 gene. In addition, the Examiner contends that the specification does not describe a strain that produces a mammalian-

like N-glycan which contains fewer than five mannose residues in the presence or absence of the endogenous OCH1 gene.

Applicants observe that previous claim 5 is not included in the rejection. As submitted above, Applicants have amended claim 1 to incorporate the features of previous claims 5-6. Present claim 1 specifically delineates the genetic modifications contained in the strain. Applicants have also amended claim 1 to delete the characterization of the mammalian-like N-glycan as containing five or fewer mannose residues. Applicants respectfully submit that the presently claimed subject matter is adequately described in the specification. Accordingly, Applicants respectfully submit that the written description rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-27 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the enablement requirement.

The Examiner admits that the specification provides an enabling disclosure for a genetically engineered strain that has a disrupted OCH1 gene and is transformed with an α-1,2-mannosidase, a GnT1 and a GalT, which enables the production of a glycoprotein comprising a specific mammalian-like N-glycan structure. However, the Examiner contends that the specification does not provide enablement for the subject matter as broadly claimed. Specifically, the Examiner states on page 11, middle paragraph of the Action, that the specification does not teach the genetic modifications required for a strain to produce a mammalian-like N-glycan structure in the presence of the endogenous OCH1 gene. In addition, the Examiner contends that the specification does not teach a strain that produces a mammalian-like N-glycan which contains fewer than five mannose residues in the presence of the

endogenous OCH1 gene or in the absence of the enzymes required to make the desired carbohydrate modifications.

Applicants respectfully submit that the foregoing amendments to the claims have adequately addressed the Examiner's rejection. Specifically, present claim 1 delineates the genetic modifications contained in the strain. Claim 1, as amended, also does not include the characterization of "five *or fewer* mannose residues" particularly objected to by the Examiner. Applicants respectfully submit that the presently claimed subject matter is fully supported by the specification, and is also consistent with the scope acknowledged by the Examiner as enabled. Accordingly, Applicants respectfully submit that the enablement description rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-27 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Gerngross et al. (U.S. 7,029,872).

Applicants respectfully submit that Gerngross et al. do not provide adequate teaching to anticipate the invention as presently claimed. In the first instance, the reference is merely a compilation of prophetic statements and discussion of numerous potential options to obtain a human-like glycosylation pattern in eukaryotic organisms. However, given the complex and distinct glycosylation pathways in various eukaryotic organisms, this reference cannot be viewed as providing clear guidance to serve as an anticipatory reference.

Applicants respectfully direct the Examiner's attention to the fact that claim 1 now specifies the strain to co-express α-1,2-mannosidase, GnT1 and GalT or functional parts thereof. The Gerngross et al. reference may have disclosed in separate contexts the expression of α-1,2-mannosidase, GnT1, and GalT, respectively, among numerous other potential enzymes to be expressed. However, the reference does not *specifically* disclose a single strain of

methylotrophic yeast that expresses all of α-1,2-mannosidase, GnT1 and GalT, and has the genomic OCH1 gene disrupted.

Furthermore, Gerngross et al. teach that $Man_5GlcxNAc_2$ must be produced in the correct isomeric form by α-1,2-mannosidase in order to provide a suitable substrate for GnT1 (col. 11, lines 5-28). The reference states that the correct isomeric form must be produced at high yield, >30% of all the isomeric forms produced. The reference goes on to suggest that this may be achieved by using an α-1,2-mannosidase that has optimal activity at a pH of between 6.5 and 7.5, equivalent to that found in the Golgi (col. 13, line 53 to col. 14, line 35). However, the reference provides no evidence that the correct isomeric form of $Man_5GlcNAc_2$ was in fact produced from any strain.

Moreover, according to the teaching of Gerngross et al., *T. reesei* α-1,2-mannosidase would not be a suitable enzyme for use in methylotrophic yeast such as *Pichia pastoris*, as its optimal activity is at a pH of 5.0 (Table on col. 14). However, the present invention demonstrates that a strain expressing a *T. reesei* α-1,2-mannosidase produced $Man_5GlcNac_2$ that accounted for more than 90% of the total N-glycan pool (see Example 3, pages 31-32 of the present specification), and that properly served as substrate for GnT1 to produce $GlcNAcMan_5GlcNac_2$ (Example 4, pages 32-33).

In order to highlight the distinguishing features of the present invention, Applicants have amended claim 1 to define the α-1,2-mannosidase as a *T. reesei* α-1,2-mannosidase. Applicants respectfully submit that Gerngross et al. do not teach, in fact, Gerngross et al. teach away from, a strain that co-expresses a *T. reesei* α-1,2-mannosidase, GnT1 and GalT, and that produces a mammalian-like N-glycan structure. Therefore, it is respectfully submitted that Gerngross et al. do not teach the claimed invention. The rejection under 35 U.S.C. §102(e) based

on Gerngross et al. is therefore overcome. Withdrawal of the rejection is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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